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(54) Title: PROCESS FOR THE PRODUCTION OF SALTS OF ERYTHROMYCIN, ROXITHROMYCIN, CLARITHROMYCIN AND AZITHROMYCIN

(57) Abstract

N-acetylcysteine, carboxymethylcysteine and thiazolidincarboxylic acid salts of erythromycin-2-propionate are produced by charging erythromycin-2-propionate and the sulphur-containing acid into a reactor. The reactants are homogenised and milled under nitrogen for 1 - 2 hours at 10 - 20 °C. To this mixture purified water is added under nitrogen and the resultant aqueous mixture is further homogenised and milled for 1 to 2 hours at 10 - 30 °C under nitrogen to produce a suspension of the desired salt. The suspension is dried under vacuum to produce a high yield of the desired salt at high levels of purity. Carboxymethylcysteine, N-acetylcysteine and thiazolidin-carboxylic acid salt of erythromycin, clarithromycin, roxithromycin and azithromycin may be produced in a similar manner.

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PROCESS FOR THE PRODUCTION OF SALTS OF ERYTHROMYCIN, ROXITHROMYCIN, CLARITHROMYCIN AND AZITHROMYCIN

Introduction

The present invention relates to a new process for the production of antibiotic and mucolytic salts of erythromycin, roxithromycin, clarithromycin, azithromycin, and propionyl esters of erythromycin.

The therapeutical properties of such salts has been partly described in EP 0057489A. The process for producing these salts as described in EP 0057489A is characterised in that the reaction is carried out in an organic solvent and in the presence of water in an amount not greater than 20%. Salts produced by this process include impurities and side products such as decomposition compounds of erythromycin (8,9-anhydrous-hemiketal) and oxidation compounds of N-acetylcysteine (N,N-diacetyl-cystine). Thus, the quality of salts produced by the process of the prior art is not sufficient for pharmaceutical preparations.

It is an object of the present invention to provide a process for the production of the above-mentioned antibiotic and mucolytic salts which overcomes at least some of these problems.

Statements of Invention

According to the invention there is provided a process for preparing a compound of the formula

X - R

wherein X is a radical selected from a group of compounds comprising sulphur containing acids,

and wherein R is a radical selected from:-

erythromycin, clarithromycin, roxithromycin, azithromycin, and a propionyl ester of erythromycin,

the process comprising reacting X with R in the presence of water in an inert atmosphere.

In one embodiment of the invention X and R are initially homogenised prior to the addition of water. Preferably X and R are homogenised for a period of from 1 to 2 hours.

In one embodiment of the invention the initial homogenisation of X and R is carried out in an inert atmosphere. Ideally water is added to the reactants in an inert atmosphere.

In a particularly preferred embodiment of the invention the reaction mixture including water is homogenised during the reaction step.

Preferably the reaction mixture is homogenised for a period of from 1 to 2 hours. Most preferably the reaction mixture is homogenised at a temperature of from 10°C to 30°C.

In one embodiment of the invention the reactants are milled to break up any particulate matter. Preferably the reactants are milled during a homogenisation step.

The inert atmosphere typically comprises nitrogen gas.

X may be a radical selected from:-

acetylcysteine, carboxymethylcysteine and thiazolidin-carboxylic acid.

The invention also provides a compound X-R as defined above whenever produced by the process of the invention.

Detailed Description of the Invention

Example

Salts of erythromycin-2-propionate with N-acetylcysteine.

327.5 Kg of erythromycin-2-propionate and 76.28 Kg of N-acetylcysteine were charged under nitrogen into an INOX vacuum dryer, Model IUT. The reactants were homogenised and milled under nitrogen for 1-2 hours at 10-20°C. To this mixture, 150 L of purified water was added under nitrogen and the resultant aqueous mixture was further homogenised and milled for 1-2 hours at 10-30°C under nitrogen to produce a suspension of the desired salt. The suspension was then dried under vacuum at 20-50°C. A yield of between 96 and 98.2% (430-440 Kg) was obtained.

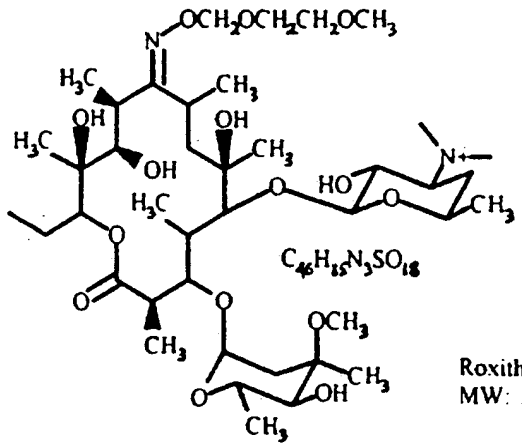
The carboxymethylcysteine, N-acetylcysteine and thiazolidin-carboxylic acid salts of erythromycin, clarithromycin, roxithromycin and azithromycin are produced in a similar manner to that described in the above example. A similar process may also be used for the production of carboxymethylcysteine and thiazolidin-carboxylic acid salts of erythromycin-2-propionate. Some of these compounds are illustrated in the Appendix.

The process described above allows the described compounds to be produced, without any solvent, in large quantities in almost quantitative yields without increased amounts of impurities and side products.

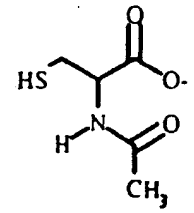
The reactors sold under the Trade Mark INOX are ideally suited for carrying out the process of the invention. Such reactors are described in US4674692 and US4506838. In particular, the INOX models IST, IHT and IUT are particularly suited for carrying out the process of the invention. These reactors are essentially vacuum-dryer reactors having a paddle rotating concentrically about an axis of the reactor which homogenises and agitates the contents of the reactor. The reactors may include a chopping and milling tool rotatably mounted on one of the paddles for rotation together therewith. The rotational action of both the paddle and the tool ensure complete mixing and milling of the contents of the reactor, ensuring that all lumps of material are uniformly broken down and homogenised with the other materials in the reactor. In some of the models mentioned above, the drying chamber may be rotated. The model IUT mentioned above may include a granulating unit comprising a series of spray nozzles located at a back end of a paddle ensuring an even distribution of liquid to be granulated.

The invention is not limited to the examples hereinbefore described but may be varied in both operational sequences and parameters without departing from the spirit of the invention.

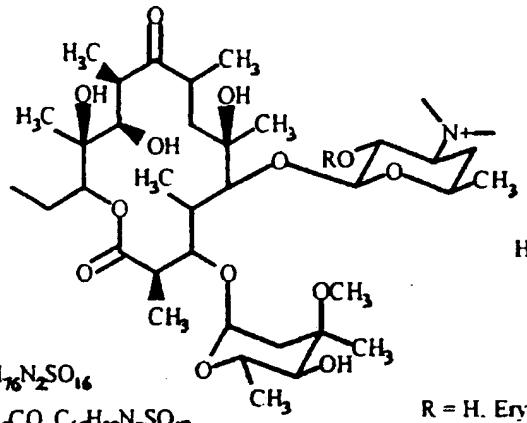
APPENDIX



$C_{46}H_{85}N_3SO_{18}$

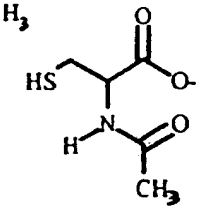


Roxithromycin-Stinoprate
MW: 1000.27

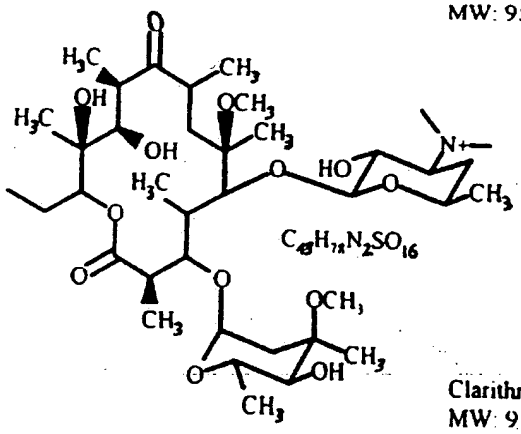


R = H. $C_{42}H_{76}N_2SO_{16}$

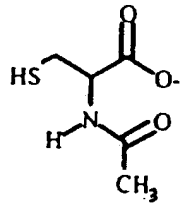
R = CH_3CH_2CO. $C_{45}H_{80}N_2SO_{17}$



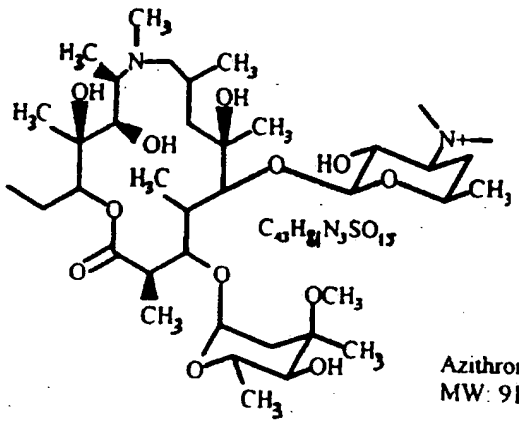
R = H. Erythromycin-Stinoprat MW: 897.12
R = CH3CH2CO. Erythromycin-2-propionate-Stinoprat
MW: 953.18



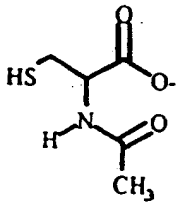
$C_{43}H_{78}N_2SO_{16}$



Clarithromycin-Stinoprat
MW: 911.16



$C_{43}H_{81}N_3SO_{15}$



Azithromycin-Stinoprat
MW: 912.19

CLAIMS

1. A process for preparing a compound of the formula

X - R

wherein X is a radical selected from a group of compounds comprising sulphur containing acids,

and wherein R is a radical selected from:-

erythromycin, clarithromycin, roxithromycin, azithromycin, and a propionyl ester of erythromycin,

the process comprising reacting X with R in the presence of water in an inert atmosphere.

2. A process as claimed in claim 1 wherein X and R are initially homogenised prior to the addition of water.

3. A process as claimed in claim 2 wherein X and R are homogenised for a period of from 1 to 2 hours.

4. A process as claimed in claim 2 or 3 wherein X and R are homogenised at a temperature of from 10 to 20°C.

5. A process as claimed in any of claims 2 to 4 wherein the initial homogenisation of X and R is carried out in an inert atmosphere.

6. A process as claimed in any preceding claim wherein water is added to the reactants in an inert atmosphere.

7. A process as claimed in any preceding claim wherein the reaction mixture including water is homogenised during the reaction step.

8. A process as claimed in claim 7 wherein the reaction mixture is homogenised for a period of from 1 to 2 hours.

9. A process as claimed in claim 7 or 8 wherein the reaction mixture is homogenised at a temperature of from 10°C to 30°C.

10. A process as claimed in any preceding claim wherein the desired compound is dried under vacuum.

11. A process as claimed in claim 5 wherein the desired compound is dried under vacuum at 20 to 50°C.

12. A process as claimed in any preceding claim wherein the inert atmosphere comprises nitrogen gas.

13. A process as claimed in any preceding claim wherein X is a radical selected from:-

acetylcysteine, carboxymethylcysteine and thiazolidin-carboxylic acid.

14. A process substantially as hereinbefore described with reference to the accompanying example.

15. A compound of the formula

X - R

in which X and R are as defined in claim 1 whenever produced by a process of any of claims 1 to 14.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/IE 97/00056

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07H17/08 C07H17/00

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07H

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 19489 A (RUSSINSKY LTD ;SCHICKANEDER HELMUT (IE); NIKOLOPOULOS AGGELOS (IE)) 27 June 1996 see page 3, line 18 - page 4, line 5; claims 7,9	1-15
X	EP 0 057 489 A (REFARMED RECH PHARM MED) 11 August 1982 cited in the application	15
A	see the whole document	1
A	FR 2 561 105 A (EDMOND PHARMA SRL) 20 September 1985 see the whole document	1
A	US 4 563 443 A (GOBETTI MARINO ET AL) 7 January 1986 see example 4	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of theinternational search	Date of mailing of the international search report
2 December 1997	09/12/1997

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 096 013 A (NUOVO CONSOR SANITAR NAZIONALE) 7 December 1983 see the whole document	1
A	US 4 826 820 A (BRAIN EDWARD G) 2 May 1989 see the whole document	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr...onal Application No
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